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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/731,741	12/10/2003	Thomas M. Schmitt	2223-171	5362

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BERESKIN AND PARR
40 KING STREET WEST
BOX 401
TORONTO, ON M5H 3Y2
CANADA

EXAMINER	
SINGH, ANOOP KUMAR	
ART UNIT	**PAPER NUMBER**
1632	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/731,741	SCHMITT ET AL.	
	Examiner	Art Unit	
	Anoop Singh	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 May 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4,10-13,17 and 22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-2, 4,10-13, 17, 22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The amendments to the claims filed on May 18, 2007 have been entered. Claims 3, 5-9, 14-16, 18-21 and 23-49 have been canceled, while claims 1, 12 and 22 have been amended. Claims 1-2, 4, 10-13, 17 and 22 are currently under consideration.

Withdrawn-Specification

The objection to the disclosure is withdrawn in view of amendments to the specification specifically removing the URLs cited on page 16, lines 283, page 52, line 6 of the specification

Claim Rejections - 35 USC § 112

Claim 22 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn in view of amendments to the claim.

Withdrawn-Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 12-13, 17 and 22 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn. Examiner would agree that it was generally known in the art that stem or progenitor cells capable of forming T cells could be modified by transfection or transduction and differentiate into cells of the T cell linage.

Maintained-Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 2, 4,10-13, 17 and 22 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. These claims recite "an *in vitro* system". The metes and bound of a "system" are unclear because system claims are not distinctly product, product by process, or method claims, therefore the interpretation of a "system" can vary considerable. Furthermore, in the instant case, it is not apparent whether an *in vitro* system is a product or product by process or process claims, particularly since system-comprising cell produces a T cell of a specific or multiple linages. In addition, it is further unclear as to what else comprises in the system comprising cell preparation other than OP9-DL-1. In addition, cell preparation comprising OP9 stromal cell in different growth condition may have variable effects depending on presence and/or absence of cytokine and/or growth factors. It is further unclear since T cell with specific markers set forth in the claim is produced using the method recited in claim 22. The metes and bound of the claimed invention is not clear. Claims 2, 4, 10-13, 17 directly or indirectly depend on claim 1. Appropriate correction is required.

Response to Arguments

Applicant's arguments filed on May 18, 2007 have been fully considered but they are not fully persuasive. Applicants in their argument state, applicant has amended claim 1 to clarify that the *in vitro* system is a system "for forming cells of the T cell lineage from stem cells or progenitor cells". In addition, applicants assert that a product that comprises a cell preparation comprising a cell preparation comprising OP9 cells modified to express a DL-1 or DL-4 notch ligand.

In response, it is noted that as amended metes and bounds of claim 1embracing an *in vitro* system for forming cells of the T cell linage from stem or progenitor cells is unclear because system claims are not distinctly product, product by process, therefore

the interpretation of a "system" could still vary considerable. It is also noted that system-comprising cell produces a T cell of multiple lineages. Therefore, it is unclear as to *in vitro* system comprising OP9-DL-1 under other conditions or produced by different process using different growth factor would have same or variable effects. It is emphasized that more clearly reciting the culture comprising OP9-DL-1 would address the basis of the rejection.

Withdrawn-Claim Rejections - 35 USC § 103

Claims 12-13 and 17 rejected under 35 U.S.C. 103(a) as being unpatentable over Jaleco et al (2001, J. Exp. Med. 194:991-1001, IDS), Nakano et al (1994, Science 265:5175 IDS) and Tatsumi et al. (1990, Proc. Natl. Acad. Sci. 87:2750-2754, IDS) is withdrawn in view of amendments to claim 12. It is noted that applicants have amended claims to include structural and functional limitation that distinguishes T cells obtained by the method of claims 12-13 and 17 from the cited prior art that fails to explicitly or implicitly discloses the specific T cell linage recited in the rejected claims.

Maintained-Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 2 and 4 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Jaleco et al (2001, J. Exp. Med. 194:991-1001, IDS), Nakano et al. (1994, Science 265:5175 IDS) and Tatsumi et al. (1990, Proc. Natl. Acad. Sci. 87:2750-2754, IDS).

Jaleco et al. provides guidance on an *in vitro* system comprising stromal cells the Delta-1 ligand, which supports T cell lymphopoiesis of human hematopoietic progenitor cells (HPCs) but does not support B cell lymphopoiesis (Abstract). Specifically, Jaleco et al. teaches that culturing HPCs with mouse S-17 stromal cells that express Delta-1 inhibits B cell differentiation and produces CD3+ CD4+CD8+ T cells (pg. 992, Materials and Methods; pg. 995, Table 1). Abbas et al. teaches that T cells that are CD3+ CD4+CD8+ have inherently undergone TCR V(D)J rearrangement {Abbas et al., (1994) Cellular and Molecular Immunology 2nd ed., 1-457; pg. 176, Fig. 8-5; pg.178 col. 1}. Jaleco et al teaches that transfecting S-17 stromal cells specifically blocks B cell lymphopoiesis (Abstract). Further, Jaleco et al. teaches that the immature T cells were separated from the aggregate population of cells (pg. 995, Table 1). Jaleco et al. does not teach using OP-9 stromal cells or inducing lymphopoiesis in mouse cells.

Nakano et al. supplements the guidance of Jaleco et al. by teaching the use of mouse OP-9 stromal cells (which inherently does not express M-CSF) to generate lymphohematopoietic cells (Abstract). Nakano et al. teaches that it is advantageous to use stromal cells lacking M-CSF when studying lymphopoiesis because the presence of M-CSF can inhibit the differentiation of ES cells to blood cells other than macrophages. However, Nakano et al do not teach transfecting OP-9 cells.

Tatsumi supplements the guidance of Jaleco et al. by teaching an *in vitro* system for studying the differentiation of mature mouse T cells from CD3- CD4-CD8- precursors by culturing them with mouse stromal cells (Abstract; pg. 2750, Materials and Methods). However, Tatsumi et al do not teach culturing OP-9 cells.

Based on the guidance provided by Jaleco et al. on an *in vitro* system comprising stromal cells the Delta-1 ligand, which supports T cell lymphopoiesis of HPCs but does not support B cell lymphopoiesis and the teachings of Nakano et al. on the advantages of using OP-9 cells when studying lymphopoiesis, it would be *prima facie* obvious to the person of ordinary skill in the art at the time the invention was made to modify the teachings of Jaleco et al. by replacing the mouse S-17 stromal cells with OP-9 cells. Further it would be *prima facie* obvious to the person of ordinary skill in the art at the time the invention was made to use the assay system of Jaleco et al. with the OP-9

cells of Nakano et al. to study mouse T cell differentiation with the mouse precursor cells using the precursors taught by Tatsumi et al.

A practitioner in the art would be motivated to modify the method of Jaleco et al. with the OP-9 cells of Nakano et al. in order to reduce the number of inhibitory ligands and to optimize T cell induction. Further, the practitioner would be motivated to use this system to study mouse T cell lymphopoiesis in order to optimize the number of T cells and variety of sub-types induced. The person of ordinary skill in the art would have a reasonable expectation of success because the modifying the teachings of Jaleco et al. by replacing the S-17 stromal cells with the OP-9 cells of Nakano et al. would have been a routine modification in the art at the time of filing. Further, the use of mouse hematopoietic precursor cells, such as those taught by Tatsumi et al. instead of human hematopoietic precursors would have been a routine modification in the art at the time of filing.

Response to Arguments

Applicant's arguments filed 05/18/2007 have been fully considered but they are not fully persuasive.

Applicant argues Jaleco et al uses S17 cell line that was known to induce two cell lineages from CD34+ precursor cell. Applicants assert that stromal cell line employed by Jeleco induced fewer cells types than that reported by Nakano. Applicants argue that one in art would not be motivated to modify the method of Jaleco with the cells of Nakano et al as this would not appear to reduce the number of inhibitory ligands as additional cell types are induced. Applicant also argues that Nakano do not provide motivation to modify Jeleco to one of ordinary to optimize the T cell induction. Applicants also assert that it is not obvious that what effect of expression of DL-1 or DL-4 would have on these cells. Only Tatsumi et al teaches the generation of mature T cell from precursor cell that are neither stem nor progenitor cells. Therefore, none of the

cited references was able to achieve the generation of mature T cell using stem or progenitor cell.

In response, it is noted claims 1-2 and 4 are interpreted as product comprising co culture of OP9 cells that have been modified to express DL-1 or DL-4 that supports T cell lymphopoiesis of any stem or progenitor cells. Thus claims are drawn to an *in vitro* system that supports T cell lymphopoiesis. T cell lymphopoiesis includes all precursors, immature and mature T cells, as recognized by the specification (pg. 19, lines 5-15). It is well established in case law that a reference must be considered not only for what it expressly teaches, but also for what it fairly suggests. In re Burkel, 201 USPQ 67 (CCPA 1979). Furthermore, in the determination of obviousness, the states of the art as well as the level of skill of those in the art are important factors to be considered. The teaching of the cited references must be viewed in light of these factors. In the instant case , Jaleco et al. teaches an *in vitro* culture to produce $CD3^+$ $CD4^+$ $CD8^+$ T cells (pg. 992, col. 1, pgph 3; pg. 992, Materials and Methods; pg. 995, Table 1). Therefore Jaleco et al teaches an *in vitro* system supports T cell lymphopoiesis. In response to applicants argument that OP9 cells disclosed by Nakano does not appear to reduce the number of inhibitory ligands as additional cell types are induced and the resulting effect of expression of DL-1 or DL-4 in these cells are unknown, it is emphasized that Nakano reference does not stand alone, but should be looked in view of teaching by Jeleco rejection. The teachings of the references must be considered together. IN the instant case, Jeleco et al specifically address whether the known inhibition of B cell development induced active Notch could depend on the action of specific Notch ligand. Jeleco et al specifically show that delta-1 completely blocks the differentiation into early B cell while promoting the emergence of a population of cells with characteristics of T/NK cells (see page 992, col. 1, last para). It is emphasized that product (system) requires only cell preparations comprising culture of two-cell type and any characteristics of resulting co culture will be inherent in the teaching of such co culture. It is again noted that claims are drawn to an *in vitro* system that produces plurality of T cell subtypes, including those taught by Jaleco et al. The practitioner would be motivated to use the OP-9 cells taught by Nakano et al because the presence of M-

CSF can inhibit the differentiation of ES cells to blood cells other than macrophages. It is emphasized that a person of ordinary skill would be motivated to practice the teachings of Jaleco et al to use OP-9 cells, transfected with a vector encoding Delta-1, in order to blocks the differentiation into early B cell while promoting the emergence of a population of cells with characteristics of T/NK cells to optimize any form of T cell induction. This would be especially relevant when studying mouse T cell lymphopoiesis in order to optimize the number of T cells and variety of sub-types induced. Therefore, Jaleco et al provide guidance to use the system of co culture comprising stromal cell modified to express DL-1 in presence of stromal cell and as stated before, a person of ordinary skill would have been motivated to try other stromal cells from other species to optimize T cell induction. Based on the results achieved by Jaleco and the teachings in the supporting references, a practitioner in the art would have a reasonable expectation of success because replacing the S-17 stromal cells with OP-9 cells would have been a routine modification in the art at the time of filing particularly since Jeleco et al specifically showed that delta-1 completely blocks the differentiation into early B cell while promoting the emergence of a population of cells with characteristics of T/NK cells. It is noted that obviousness does not require absolute predictability of success; for obviousness under 35 U.S.C. § 103, all that is required is a reasonable expectation of success. See In re O'Farrell, 7 USPQ2d 1673 (CAFC 1988). Furthermore, the modified co culture would inherently show different characteristics markers depending on cells and culture condition. Given, the, the product (system) is merely required to comprise OP9 that is modified to express DL-1 and support T cell lymphogenesis of stem cell or progenitor cell. The product (in vitro system) used to generate cells of specific linage disclosed by Jaleco et al, Nakano et al and Tatsumi and those embraced by the instant claims appear to be structurally same. Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a prima facie case of either anticipation or obviousness has been established. *In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the

burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Therefore, the prima facie case can be rebutted by evidence showing that the prior ad products do not necessarily possess the characteristics of the claimed product. In re Best, 562 F.2d at 1255, 195 USPQ at 433.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Conclusion

No Claims allowed.

The following is a statement of reasons for the indication of allowable subject matter: Claims 12-13, 17 and 22 are free of art but are subject to other rejection. It is noted that combination of Jaleco et al (2001, J. Exp. Med. 194:991-1001, IDS), Nakano et al. (1994, Science 265:5175 IDS) and Tatsumi et al. (1990, Proc. Natl. Acad. Sci. 87:2750-2754, IDS) do not make instant claims obvious because method disclosed in the instant claims require differentiation of stem or progenitor cells to form T cells of specific lineage which is increased by at least about 10 to 15 fold that is not disclosed in prior art.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anoop Singh whose telephone number is (571) 272-3306. The examiner can normally be reached on 9:00AM-5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272- 4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Anoop Singh
Au 1632

/Anne-Marie Falk/
Anne-Marie Falk, Ph.D.
Primary Examiner, Art Unit 1632